



DRAFT STATEMENT
March 23, 2005
7:00 p.m.

NATIONAL INSTITUTES OF HEALTH
STATE-OF-THE-SCIENCE CONFERENCE STATEMENT
Management of Menopause-Related Symptoms
March 21–23, 2005

NIH consensus and state-of-the-science statements are prepared by independent panels of health professionals and public representatives on the basis of (1) the results of a systematic literature review prepared under contract with the Agency for Healthcare Research and Quality (AHRQ), (2) presentations by investigators working in areas relevant to the conference questions during a 2-day public session, (3) questions and statements from conference attendees during open discussion periods that are part of the public session, and (4) closed deliberations by the panel during the remainder of the second day and morning of the third. This statement is an independent report of the panel and is not a policy statement of the NIH or the Federal Government.

The statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.

1 **Introduction**

2 Menopause is a natural process in women's lives as they age. Many women go through
3 the menopausal transition with few or no symptoms, while some have significant or even
4 disabling symptoms. Menopause is defined as the permanent cessation of menstrual periods that
5 occurs naturally or is induced by surgery, chemotherapy, or radiation. Natural menopause is
6 recognized after 12 consecutive months without menstrual periods. The hormonal changes
7 during the menopausal transition can span several years. It often begins with variations in length
8 of the menstrual cycle.

9 The following three categories were defined by experts at the Stages of Reproductive
10 Aging Workshop (STRAW) in 2001:

- Reproductive stage: From menarche (first menstrual period) to the beginning of the perimenopause (when cycles become variable)
- Perimenopause: The time around menopause during which menstrual cycle and endocrine changes are occurring, including the first 12 months without periods
- Postmenopause: Begins at the time of the final menstrual period (FMP), overlapping with perimenopause by 12 months

In this report, we use the term “menopausal transition” to mean the time from late reproductive stage into postmenopause. The focus of this report is the management of menopausal symptoms, such as hot flashes, night sweats, vaginal dryness, problems with sleeping, loss of sexual desire, or urinary and bleeding problems. These symptoms vary in combination, intensity, and duration.

Estrogen either by itself or with progestins has been the therapy of choice for decades for relieving menopause-related symptoms. The Women’s Health Initiative (WHI) is a large clinical trial that was designed to see if estrogen with or without progestin therapy could prevent chronic conditions, such as heart disease and dementia. The estrogen and progestin stratum ended early because of serious health problems, including blood clots, stroke, heart disease, and breast cancer among estrogen users. These findings raised serious questions about the safety of estrogen use to treat symptoms of menopause. Many women stopped hormone replacement therapy and some searched for alternative therapies. To reflect a shift of focus from “replacement” to use of hormones for relief of symptoms, we will use the term menopause

hormonal therapy (MHT). MHT includes a range of doses and preparations of estrogen and progestin.

Women and their health care providers need to know the safest and most effective medical and nonmedical treatments for menopausal symptoms. To address this need, the National Institute on Aging and the Office of Medical Applications of Research, of the NIH, sponsored a State-of-the-Science Conference on Management of Menopause-Related Symptoms, March 21–23, 2005, in Bethesda, MD. During the first 2 days of the conference, experts presented information on the biology of the menopausal transition, the nature of the symptoms women experience, and strategies for relieving the common problems associated with the menopausal transition. After weighing all of the scientific evidence, an independent panel prepared and presented a state-of-the-science statement answering the key conference questions.

1. What is the evidence that the symptoms more frequently reported by middle-aged women are attributable to ovarian aging and senescence?

Because women age as they progress from premenopause to postmenopause, it is difficult to determine which symptoms arising during this time are due to ovarian aging specifically and which are due to general aging and/or life changes commonly experienced in midlife. Specific symptoms are discussed below.

Vasomotor Symptoms (Including Hot Flashes and Night Sweats)

The vasomotor symptoms of hot flashes—sudden sensations of intense heat with sweating and flushing typically lasting 5–10 minutes—and night sweats are reported with high frequency in perimenopausal women. There is strong evidence that menopause causes vasomotor

1 symptoms. Hot flashes rarely occur until women enter the perimenopausal transition and occur
2 in a higher percentage of women in the later phases of the menopausal transition. They also
3 occur with a higher frequency and greater severity in younger women who undergo a sudden
4 onset of menopause due to surgical removal of their ovaries or medical conditions or treatments
5 which decrease the ability of ovaries to produce hormones. Further evidence supporting this
6 association is provided by the large number of good quality interventional clinical trials
7 demonstrating improvement of vasomotor symptoms with estrogen treatment.

8 **Vaginal Dryness/Painful Intercourse**

9 Vaginal dryness, often leading to painful intercourse (dyspareunia), is reported by a
10 significant number of perimenopausal and postmenopausal women. Evidence that menopause
11 causes vaginal dryness is strong. The percentage of women experiencing vaginal dryness
12 increases throughout the menopausal transition and persists indefinitely. Increases in vaginal
13 dryness correlate well with the onset of menopause transition. Microscopic examination of
14 vaginal cells obtained from postmenopausal women complaining of vaginal dryness shows
15 changes consistent with low estrogen levels. Furthermore, treatment of vaginal dryness with
16 estrogen (either vaginal or systemic) results in relief of symptoms, including menopause
17 associated dyspareunia, for most women.

18 **Sleep Disturbance**

19 Sleep disturbances are common across the lifespan of women for a variety of reasons.
20 There is moderate evidence that menopause is the cause of such disturbances in some women. It
21 is unclear whether difficulty sleeping is due solely to vasomotor symptoms.

1 **Mood Symptoms**

2 There is an absence of evidence showing that ovarian changes associated with
3 menopause might be a cause of depression, anxiety, and/or irritability. History of prior
4 depression, life stress, and general health are the major predictors of mood symptoms during
5 midlife. Because of the multiple potential causes of mood changes and the relatively high
6 proportion of women reporting one or more of these symptoms, it is difficult to establish whether
7 menopause causes some small increase in the prevalence of mood symptoms during the
8 perimenopausal years. The evidence from estrogen treatment trials is mixed, with only weak
9 evidence of improvement in depression or anxiety relative to placebo for a small subset of
10 moderately or highly symptomatic women treated with estrogens.

11 **Cognitive Disturbances**

12 There is insufficient information to conclude any causal relationship between the
13 menopausal transition and difficulty thinking, forgetfulness, or other cognitive disturbances.
14 Existing studies are inadequate for separating aging effects from the effects of menopause.

15 **Somatic Complaints**

16 The majority of studies showed no association between the prevalence of somatic
17 complaints, including back pain, tiredness, stiff or painful joints, and menopausal status.

1 Urinary Incontinence

2 In a small number of studies, reported associations between menopausal status and
3 urinary incontinence are mixed. Current results are inadequate to demonstrate a causal
4 relationship.

5 Uterine Bleeding Problems

6 The menopausal transition is, by definition, associated with alteration in menstrual
7 cycles. In addition, menorrhagia (heavy bleeding) has frequently been reported by
8 perimenopausal women. There are no adequate long-term studies examining menorrhagia during
9 the menopausal transition. Any such studies would need to determine the presence of fibroids
10 and other uterine conditions.

11 Sexual Dysfunction

12 Two components of sexual dysfunction can be identified during the menopausal
13 transition: painful intercourse resulting from vaginal atrophy and dryness, as discussed above,
14 and changes in libido, arousal, and other aspects of sexuality. These latter changes are strongly
15 associated with age-related factors, such as changes in personal relationships, stressors, and
16 socioeconomic conditions. Causal associations with menopausal status have not been established
17 definitively.

18 Reduced Quality of Life

19 Currently, there is inadequate information to demonstrate either positive or negative
20 effects of the menopausal transition on quality of life in a general population.

1 **2. When do menopausal symptoms appear, how long do they persist and with what**
2 **frequency and severity, and what is known about the factors that influence them?**

3 **Natural History of Menopausal Symptoms**

4 Menopausal symptoms vary among women at each stage of the menopausal transition
5 and also vary for each woman over time as she goes through these stages. In the United States,
6 most women experience menopause between the ages of 40 and 58, with a median age of 52.
7 Factors associated with earlier menopause include lower body weight, shorter menstrual cycles,
8 and smoking. Higher body weight is associated with later onset of menopause.

9 Natural history concerns the symptoms which are experienced and their prevalence,
10 severity, frequency of episodes, and duration (number of years experienced). Some women who
11 transit menopause have no symptoms at all; but most experience some symptoms, often
12 beginning several years before the FMP. Understanding the natural history of menopausal
13 symptoms requires long-term data on numerous women from diverse backgrounds. To date, most
14 longitudinal studies have followed women for 2–8 years, which is not long enough to define the
15 natural history of the menopausal transition. In addition, these studies have just had one or
16 several followups and have excluded important groups of women (those with surgical
17 menopause and those who are on hormone therapy). Other major limitations of these studies are
18 that they have mainly studied Caucasian women and have asked about current symptoms only
19 (potentially missing those that occur between interviews). Most analyses consider symptoms
20 one-by-one, yet they often occur in multiples in a woman's life. Last, the age ranges of studies
21 miss most women with premature ovarian failure. Spontaneous premature ovarian failure cannot

be considered the equivalent of an early natural menopause because other disease processes may be involved that have important clinical implications.

Prevalence of Menopausal Symptoms

The following symptoms are strongly or moderately linked to menopause: hot flashes, night sweats, vaginal dryness, and sleep disturbance. Evidence about other symptoms is limited and weak (see Question 1). We state below the known symptom prevalence by menopausal stage, using ranges of estimates from prior studies. The wide ranges may reflect variability in how symptoms are measured and reported, women studied, and study quality. It is important to note that women who have had sudden menopause (e.g., surgical) are likely to have symptoms at the higher end of these ranges. Long-term assessment of symptoms into the postmenopausal period is lacking due to short followup after the FMP. Few data exist about severity, frequency, and duration of symptom episodes.

Vasomotor Symptoms (Hot Flashes and Night Sweats)

The estimates of prevalence of vasomotor symptoms varies in the premenopausal stage from 14 to 51 percent, in perimenopause from 35 to 50 percent and in postmenopause from 30 to 80 percent. Increased vasomotor symptoms are associated with high body mass index and younger age of onset of menopause. After the WHI study results were published, many women in clinical settings stopped hormone therapy. In one study, among women who discontinued hormonal therapy, 25 percent resumed it due to symptoms. This would indicate that there is a significant subgroup for which symptoms were so severe that they were willing to accept some increased risk of long-term complications.

Vaginal Dryness/Painful Intercourse

Vaginal dryness becomes increasingly more common throughout the menopausal transition. The prevalence of vaginal dryness varies in the premenopausal stage from 4 to 22 percent, in perimenopause from 7 to 39 percent, and in postmenopause from 17 to 30 percent.

Sleep Disturbance

Women appear to have more sleep disturbances as they progress through the menopausal stages. The prevalence of sleep disturbance varies in the premenopausal stage from 16 to 42 percent, in perimenopause from 39 to 47 percent, and in postmenopause from 35 to 60 percent. The postmenopausal stage includes women with either surgical or natural menopause in these studies.

Mood Symptoms

Different studies have estimated the prevalence of mood symptoms in the premenopausal stage from 8 to 37 percent, in perimenopause from 11 to 21 percent, and in postmenopause (natural or surgical) from 8 to 38 percent. African Americans may report more mood symptoms than Caucasians during the menopausal transition, but this difference narrows greatly when socioeconomic differences are controlled for in the analysis.

Other Symptoms

The prevalence of urinary complaints varies in the premenopausal stage from 10 to 36 percent, in perimenopause from 17 to 39 percent and in postmenopause (natural or surgical) from 15 to 36 percent.

No association appears to exist for increased physical complaints or cognitive problems during the menopausal transition.

Women in the age range of menopause demonstrate an increase in sexual dysfunction. The association between sexual dysfunction and vaginal dryness is unknown.

Overall, the natural history of menopausal symptoms may differ for race/ethnic groups and for women with surgically induced menopause. Current studies will provide information on the first issue, if adjusted socioeconomic differences. Women with surgical menopause, and some who cease hormone therapy, are clinically known to sometimes experience swift onset of symptoms that can be severe.

3. What is the evidence for the benefits and harms of commonly used interventions for relief of menopause-related symptoms?

A variety of treatments have been studied for management of menopausal symptoms. By far, the most intensively studied is estrogen, often in combination with progestin. Other treatments that have been studied include other hormones, antidepressants, isoflavones and other phytoestrogens, botanicals, acupuncture, and behavioral interventions.

Estrogen (Hormone Therapy)

Vasomotor Symptoms

Estrogen, either by itself or with progestins, is the most consistently effective therapy for hot flashes and night sweats. Low-dose estrogen (i.e., doses less than or equal to 0.3mg conjugated equine estrogen, 0.5mg oral micronized estradiol, 25µg transdermal estradiol, or

2.5µg ethinyl estradiol) has been shown to be effective for many women, though some women require a higher dosage for relief of hot flashes.

Estrogen therapy at doses equivalent to 0.625mg conjugated equine estrogen increases the risk of serious disease events, specifically stroke and deep vein thrombosis and/or pulmonary embolism, and when combined with the progestin (medroxyprogesterone acetate), coronary events and breast cancer. In studies in which women were treated for 5–7 years, increased risks for coronary and thromboembolic events started to emerge in the first year of use. Risks for stroke started to increase after 2 years of use. Risks for breast cancer started to increase after 3–4 years of use. While experts theorize that long-term adverse effects associated with low-dose estrogen are lower, the exact risks and benefits are not known.

Risk-benefit analyses are important for women whose vasomotor symptoms are severe and create a burden on daily life. These women may be willing to assume greater risk for the sake of reducing these symptoms.

Urogenital Symptoms

Oral estrogen, either by itself or with progestins, and a variety of vaginal estrogen preparations are beneficial for urogenital symptoms, such as vaginal dryness and painful intercourse. Results of studies are mixed regarding the effectiveness of transdermal estradiol for the management of these urogenital symptoms. Results from two large studies of oral estrogen, either by itself or with progestins, showed increased risk for the development of urinary incontinence and for its worsening in women who were already experiencing incontinence.

1 ***Other Symptoms***

2 Estrogen has also been found to be helpful for sleep disturbances and with improved
3 quality of life. There is also a suggestion that estrogen may be helpful for mood symptoms, but
4 results of these studies were mixed.

5 **Progestin**

6 There is a small amount of conflicting data regarding the efficacy of progestins for
7 treatment of hot flashes. Adverse effects have not been systematically studied.

8 **Androgens (Testosterone)**

9 Testosterone can be administered in a variety of forms, including injections,
10 subcutaneous pellets, gels, transdermal patches, and oral testosterone in combination with
11 estrogen. Studies comparing combination oral testosterone-estrogen with estrogen alone found
12 positive effects for improving libido. There were no added benefits for vaginal dryness or sleep
13 disturbances. With the exception of studies of women who had their ovaries surgically removed,
14 there are no data on the effects of other testosterone formulations. Adverse effects of testosterone
15 therapy include acne, hirsutism, and weight gain. The long-term risks of taking testosterone have
16 not been studied in this population.

17 **Dehydroepiandrosterone (DHEA)**

18 The long-term risks, benefits, and adverse effects of DHEA have not been studied in
19 large randomized clinical trials. A few small studies suggest a potential benefit for the treatment
20 of hot flashes and decreased sexual arousal. However, like many other dietary supplements, the

lack of a standard formulation or dose for DHEA limits the ability to generalize these findings and makes it a challenging therapy to study.

Bioidentical (and “Natural”) Hormones

Bioidentical hormones, often called “natural” hormones, are treatments with individually compounded recipes of a variety of steroids in various dosage forms, with the composition and dosages based on a person’s salivary hormone concentration. These steroids may include estrone, estradiol, estriol, DHEA, progesterone, pregnenolone, and testosterone. There is a paucity of data on the benefits and adverse effects of these compounds.

Tibolone

Tibolone is a synthetic steroid compound with relatively weak hormonal activity. It is not available in the United States but has been used in Europe for treatment of vasomotor symptoms, sexual dysfunction, and osteoporosis prevention for almost 20 years. Despite the widespread clinical use of this compound, there are not very many studies of its effects. These studies did suggest benefit for hot flashes and sleep disturbance. In studies comparing tibolone and estrogen, the effects were similar for hot flashes and libido; however, these were small studies.

Adverse effects of tibolone include pain, weight gain, and headache. Its association with uterine bleeding is less clearly defined. The long-term effects of tibolone, particularly in breast cancer, cardiovascular disease, and the reduction of osteoporotic fractures, are still unknown.

1 **Antidepressants**

2 A few well-designed short-term studies with small numbers of participants have assessed
3 the use of antidepressants for the treatment of hot flashes. Results have been mixed; some agents,
4 such as paroxetine and venlafaxine, may decrease hot flashes to a moderate degree and improve
5 quality of life for symptomatic women undergoing normal menopause as well as breast cancer
6 survivors. Known adverse effects for antidepressants include diminished libido, insomnia,
7 headache, and nausea. Long-term effects are unknown.

8 **Isoflavones and other Phytoestrogens**

9 A substantial number of studies of phytoestrogens and isoflavones have been conducted,
10 motivated by epidemiological data showing differences in levels of menopausal symptoms in
11 countries with different levels of these nutrients in their diets. Most of these products are not
12 manufactured in a standardized way, so they may differ in composition from trial to trial. Several
13 studies of soy extracts suggested that they may have some mitigating effect on hot flashes. Trials
14 of dietary soy are mixed; the majority of studies did not indicate benefit. Adverse event
15 information provided in these studies is very limited; long-term side effects have not been
16 investigated.

17 **Complementary and Alternative Approaches**

18 The findings of the WHI have contributed to the public's growing interest in
19 complementary and alternative approaches for the management of vasomotor symptoms. In
20 general, research on these approaches is scant and has focused to date primarily on botanicals,
21 with a few studies of other approaches.

1 **Botanicals**

2 Only a few of the botanical products on the market have been carefully studied. Progress
3 in investigating these supplements is hampered by methodological challenges, including natural
4 variability in the target botanical and other product components, variants in solvents, and
5 methods of extraction.

6 Black cohosh (*Actaea racemosa*, *Cimicifuga racemosa*) is the most studied botanical
7 product. Originally, it was thought that black cohosh had estrogenic properties, but recent work
8 suggests it does not. In the English-language literature, there is little evidence that black cohosh
9 is an effective treatment for hot flashes. However, methodological issues compromise much of
10 the existing research, and ongoing NIH trials should provide helpful data. Some cautions have
11 been raised about possible adverse effects of black cohosh on the liver, although product
12 variation and use of concomitant products make it difficult to ascertain exactly what was taken
13 when adverse events were reported.

14 Kava (*Piper methysticum*) has been shown effective in reducing anxiety, but evidence is
15 lacking with respect to its effects on hot flashes. Further, kava has been associated with damage
16 to the liver. The Food and Drug Administration has issued a warning to patients and providers
17 about potential harm.

18 Red clover leaf (*Trifolium pretense*) contains phytoestrogen compounds and is believed
19 to work as a weak estrogen in the body. However, studies suggest that it is not more effective
20 than placebo in reducing hot flashes.

1 Dong quai root (*Angelica sinensis*) is widely used for a variety of complaints, but there is
2 evidence that it is not effective for the treatment of hot flashes. There is an interaction with
3 warfarin that may lead to bleeding complications.

4 Ginseng root (*Panax ginseng*, *Panax quinquefolius*) may be helpful with respect to
5 quality-of-life outcomes, such as well-being, mood, and sleep, but does not appear to affect hot
6 flashes.

7 In general, the study of botanicals as treatments for hot flashes is still in its infancy.
8 There are major methodological problems associated with studying products that are not
9 standardized. Basic research on dosing, factors that affect the metabolic processes of these
10 products, and mechanisms of action is needed for this area of investigation to move forward on a
11 solid foundation.

12 Overall, there is a paucity of well-designed studies of complementary and alternative
13 approaches, including acupuncture, energy modalities, mind-body approaches, homeopathy, and
14 manipulative and body-based practices, in addition to approaches from other healing systems,
15 including traditional Chinese medicine and ayurvedic medicine. Although there are a number of
16 published studies on a variety of botanicals, most have important limitations that make their
17 findings unclear.

18 **Behavioral Interventions for Hot Flashes and Other Menopausal Symptoms**

19 Behavioral interventions may be an important area of investigation for the treatment of
20 menopause-related symptoms because adverse effects are rare. However, the effectiveness of

such interventions has not yet been demonstrated in large, well-controlled studies. In several small studies:

- Exercise resulted in improved quality of life, but not in positive change of vasomotor symptoms, vaginal dryness, or other menopause-related symptoms.
- Health education resulted in improved knowledge about menopause and menopause-related symptoms, but not change in the symptoms themselves.
- Paced respiration (a type of slow, deep breathing, requiring training) for hot flashes showed early promise in a very small group of patients.

4. What are the important considerations in managing menopause-related symptoms in women with clinical characteristics or circumstances that may complicate decisionmaking?

Decisionmaking for women regarding treatment of menopausal symptoms requires balancing of potential benefits against potential risks. Women at high risk for serious medical outcomes with the use of estrogen include those with a history of breast cancer, those with an elevated risk of breast and/or ovarian cancer based on genetic factors and/or family history, and women who have, or are at high risk for, cardiovascular disease. Women with these risk factors may be particularly motivated to seek nonhormonal therapies to treat menopausal symptoms. A few small studies in breast cancer survivors suggest that some antidepressants (such as venlafaxine) can effectively treat vasomotor symptoms in women with breast cancer; other treatments, including clonidine and megestrol acetate, have also shown positive effects in a few studies. These treatments have their own adverse effects (such as low libido, nausea, dry mouth,

1 or constipation) that need to be weighed against the potential benefits. The long-term safety of
2 these agents in women with breast cancer has not been studied. Given the potential for estrogenic
3 actions, the long-term safety of phytoestrogens for women in this category remains unknown.
4 Vaginal estrogen preparations to treat vaginal dryness and pain with intercourse may also be an
5 attractive option for these women. Such topical therapies are known to increase circulating
6 estrogen levels, but by much smaller amounts than oral estrogen therapy. Because these topical
7 therapies have not been studied in large numbers of women for long periods of time, actual
8 levels of risk for long-term complications, such as breast cancer recurrence, while likely much
9 lower than for oral therapy, are not fully known.

10 Women who have had their ovaries surgically removed (surgically induced menopause)
11 often experience more severe symptomatology, including hot flashes and sexual dysfunction.
12 Benefits and risks of estrogen therapy in these women are generally similar to those found in
13 studies of other women who have had hysterectomies and are taking estrogen. Risks may be
14 elevated, however, in women whose oophorectomies were performed specifically to treat or
15 prevent cancer.

16 In women who have undergone an oophorectomy and a hysterectomy, some studies
17 suggest that oral or transdermal testosterone improves sexual function and psychological well-
18 being, though definitive studies are lacking. These studies did not demonstrate a benefit for
19 testosterone for the treatment of hot flashes, vaginal dryness, sleep disturbances, or mood.

1 **5. What are the future research directions for treatment of menopause-related symptoms**
2 **and conditions?**

3 The future research direction for the treatment of menopausal symptoms is multifaceted
4 and can be categorized as conceptual, methodological, treatment-oriented, and research targeted
5 at improving quality of care.

6 **Conceptual**

7 A conceptual framework is needed to link the most prevalent menopausal symptoms to
8 genetic, neurochemical, neurobiological, and physiologic factors and reproductive surgical or
9 medical treatments hypothesized to cause symptoms, and the social and cultural context in which
10 women experience them. Testing of the hypothesized associations in the model will delineate
11 which symptoms are closely associated with hormonal changes and which are not and may
12 identify novel nonhormonal treatments targeted to specific neurochemical and biochemical
13 pathways for the most bothersome symptoms.

14 **Methodological**

15 Reliable and valid data collection instruments of the most prevalent menopausal
16 symptoms are needed, and the research community should be given incentives to use the same
17 standardized measures across studies. These instruments need to be developed and validated in
18 non-English languages. A standardized set of measurement tools for specific domains should be
19 developed for use in federally funded studies and encouraged in all studies. Standardized
20 approaches for the assessment of vasomotor symptoms and urogenital symptoms will greatly
21 facilitate the comparison and pooling of results across studies.

1 In many of the large, well-designed clinical trials, menopausal symptoms, such as hot
2 flashes, improved in 30–35 percent of women in the placebo arms of the studies. This high rate
3 of resolution of symptoms may be part of the natural progression of menopausal symptoms or
4 ancillary treatments, or may be due to self-care practices, regression to the mean, or other
5 measurement issues. Because of this very consistent finding across many trials, it is critical that
6 all evaluations of new treatments are rigorously compared in randomized designs where there is
7 a suitable placebo or control arm, blinded when feasible.

8 Improved statistical approaches are needed for the design and analysis of both
9 longitudinal observational studies and clinical trials of treatments.

10 To date, the vast majority of longitudinal data that describe menopausal symptoms and
11 the effectiveness of treatments have been collected primarily among Caucasian women. This
12 raises critical questions about the ability to generalize findings from these studies to women from
13 multiple ethnic and racial groups who reside in the United States. Therefore, it is critical that all
14 future observational studies enroll populations that allow for estimation of the effect in the target
15 population, and treatment trials for menopausal symptoms recruit sufficient numbers of ethnic
16 and racial groups of women to conduct subgroup analyses.

17 Systematic monitoring for adverse events needs to be implemented in all treatment trials
18 and both methods of monitoring and safety findings need to be included in study reports.

19 **Treatment-Oriented**

20 New research is needed that will describe the patient characteristics and self-care
21 behaviors that are associated with fewer bothersome symptoms and better quality of life during

1 the menopausal transition. What physical, emotional, and social characteristics predict this
2 resilience? What attributions do these women make about their bodies, aging, symptoms, and
3 quality of life? Research is also needed about nonmedical treatments, including behavioral
4 treatments and complementary and alternative approaches to menopausal symptom management.

5 Longer-term followup studies are needed to gain a better understanding of the natural
6 history of symptom trajectories 15–25 years after menopause. We also need to learn more about
7 the minority of women who experience debilitating menopausal symptoms that affect their
8 quality of life and functioning and are most in need of safe treatments. The ideal observational
9 studies would follow a diverse population of women for several decades, with frequent
10 followups, few exclusion criteria, and full symptom histories, including the time between
11 interviews. Data for the normal course of symptoms (namely, for women with natural
12 menopause who take no menopause-related medications) are a crucial baseline for comparison
13 with special subgroups, such as women with surgical menopause.

14 Little is known about major adverse events that could be associated with 3-to-5-year
15 exposures to low-dose estrogen and progestins for the treatment of moderate-to-severe
16 menopausal symptoms. Particular attention needs to be paid to the measurement of thrombotic
17 and cardiovascular events and breast cancer that may occur 5–10 years after a 3-to-5-year
18 exposure to low-dose hormones. A new treatment trial is needed of symptomatic multiethnic
19 sample of women in the menopausal transition with adequate representation over a range of body
20 mass indices, designed to address the ideal dose, most appropriate duration, and methods for
21 tapering off of hormone therapy, and long-term adverse events. A randomized clinical trial is
22 needed to assess the long-term safety of locally applied estrogens for vaginal dryness and

dysparenia in survivors of breast cancer. Clinical trials for the management of menopausal symptoms are also needed for women who have had prophylactic oophorectomy. Further investigations need to be performed to determine the efficacy and safety of testosterone monotherapy for the treatment of sexual dysfunction.

The newer classes of antidepressants, selective serotonin reuptake inhibitors, and serotonin and norepinephrine reuptake inhibitors show some promising early results for the treatment of vasomotor symptoms, mainly among breast cancer survivors. However, adequately powered, longer (at least 1 year) randomized clinical trials are needed to study the longer-term effectiveness of medications, such as venlafaxine and paroxetine, and more fully measure the adverse effects, such as decreased libido, nausea, insomnia, and headaches. Additionally, smaller physiologic studies are needed to better understand which medications in these classes may decrease the effectiveness of tamoxifen and other selective estrogen receptor modulators (SERM) that are used in breast cancer survivors.

A large barrier to identifying whether any of the dietary supplements are effective for treating menopause is due to the lack of regulation of the various preparations. This has led to large differences in the content of active ingredients in various preparations. A critical first step is to establish batch-to-batch consistency and conduct dose-ranging studies prior to conducting Phase 2 and 3 trials to determine proof of concept and efficacy. Ultimately, clinical trials of these agents will be needed, but it is premature to recommend these until the steps above have been accomplished.

Cross-national studies of menopause symptoms and their management are welcome additions to U.S. data. Besides self-reports, they could include objective measures of vasomotor

1 symptoms. This would help elucidate how much differences in symptom experience are based on
2 physiologic manifestations versus cultural differences in symptom perception, evaluation, and
3 reporting.

4 **Quality of Care**

5 Tools are needed to assist health care providers and women with the estimation of
6 absolute rather than relative risk of hormonal therapy during the clinical encounter.

7 Large-scale data showing the normal course of symptoms for women with natural
8 menopause who use no drugs serve as a crucial baseline for comparison with those two groups.

9 **Conclusions**

- 10 • Menopause is the permanent cessation of menstrual periods that occurs naturally
11 around age 52. Many women have few or no symptoms; these women are not in need
12 of medical treatment.
- 13 • Premenopausal or perimenopausal women who have menopause induced by surgery,
14 chemotherapy, or radiation are more like to experience bothersome and even
15 disabling symptoms. These women deserve safe and effective treatment.
- 16 • It is difficult to determine which symptoms are truly associated with menopause as
17 opposed to aging.
- 18 • Vasomotor symptoms are reported with high frequency. Estrogen, either by itself or
19 with progestins, is the most consistently effective therapy for these symptoms.
20 However, the WHI has identified a defined risk of these therapies. Decisionmaking

1 for women regarding treatment for menopausal symptoms requires personal
2 knowledge and balancing of these risks.

- 3 • There are many potential alternatives to estrogen. However, their effectiveness and
4 long-term safety need to be studied in rigorous clinical trials in diverse populations of
5 women.
- 6 • To address the charge to this panel, much more research is needed to clearly define
7 the natural history of menopause, associated symptoms, and effective and safe
8 treatments for bothersome symptoms. Natural histories are important for both science
9 and policy. Knowing how many women transit menopause with few symptoms, and
10 how many manage menopause largely on their own, can lead to public health
11 information that empowers women and increases their self-reliance. Medical care and
12 future clinical trials are best focused on women with the most severe and prolonged
13 symptoms.
- 14 • The state of the science in management of menopausal symptoms should be
15 reassessed periodically.

16 Menopause is “medicalized” in contemporary American society. Knowing how many
17 women transit menopause with no or mild symptoms, and how many women handle menopause
18 largely on their own, can lead to public health information that empowers women and increases
19 their self-reliance. Medical care is best focused on women with the most severe and prolonged
20 symptoms, and barriers to that care should be removed. There is great need to develop and

- 1 disseminate information that emphasizes menopause as a normal, healthy phase of women's
- 2 lives.
- 3

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